PATENT
Docket No. 432722002612

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Rhea Amid

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Gregory R. MUNDY *et al.*

Serial No.: To be assigned

Divisional of Serial No. 09/695,807

Filing Date: Herewith

For: INHIBITORS OF PROTEASOMAL ACTIVITY FOR STIMULATING BONE AND HAIR GROWTH

Examiner: To be assigned

Group Art Unit: To be assigned

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to the examination of the above-captioned application, please amend the application as follows.

IN THE SPECIFICATION:

At page 1, after the title, lines 4-8, please replace the first paragraph with the following new paragraph:

--This application is a divisional of U.S. Serial No. 09/695,807, filed October 23, 2000, now pending, which is a continuation-in-part of U.S. Serial No. 09/421,545, filed 20 October 1999, now pending, which is a continuation-in-part of U.S. Serial No. 09/361,775, filed 27 July 1999, now pending, which is a continuation-in-part of U.S. Serial No. 09/113,947, filed 10 July 1998, now pending. The contents of these applications are incorporated herein by reference.--

IN THE CLAIMS:

Please cancel claims 1-24, 26 and 28-44 without any prejudice and disclaimer.

Please replace claim 25 with the following clean set of amended claim 25. A mark-up version of the amended claim 25 is attached hereto as Exhibit A.

25. (Amended) A method to treat a mammalian subject for a condition benefited by stimulating hair growth which method comprises administering to said mammalian subject in need of such treatment an effective amount of a compound that inhibits proteasomal activity or that inhibits production of proteasome proteins.

Please add new claims 45-70 as follows:

45. (New) The method of claim 25, wherein the compound inhibits the chymotrypsin-like activity of the proteasome.

46. (New) The method of claim 45, wherein the compound is a peptide having at least 3 amino acids and a C-terminal functional group that reacts with the threonine residue of the chymotrypsin-like catalytic site of the proteasome.

47. (New) The method of claim 46, wherein the C-terminal functional group is selected from the group consisting of an epoxide, a $-B(OR)_2$ group, a $-S(OR)_2$ group and a -SOOR group, wherein R is H, an alkyl (C_{1-6}) or an aryl (C_{1-6}).

48. (New) The method of claim 47, wherein the functional group is an epoxide that forms a morpholino ring with the threonine residue of the chymotrypsin-like catalytic site of the proteasome.

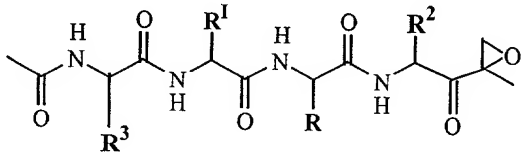
49. (New) The method of claim 45, wherein the peptide is a peptide α', β'-epoxyketone.

50. (New) The method of claim 49, wherein the peptide α', β'-epoxyketone has at least 4 amino acids.

51. (New) The method of claim 49, wherein the c-terminus amino acid of the peptide α', β'-epoxyketone is a hydrophobic amino acid.

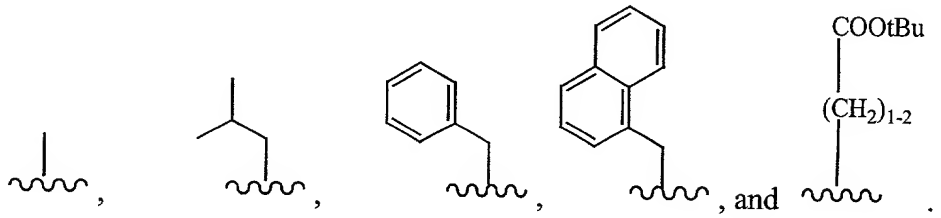
52. (New) The method of claim 51, wherein the hydrophobic amino acid is leucine or phenylalanine.

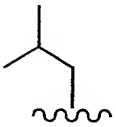
53. (New) The method of claim 49, wherein the peptide α', β'-epoxyketone has the following formula:

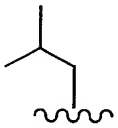
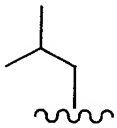


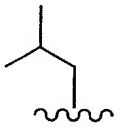
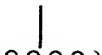
wherein each of R, R^I, R^2 and R^3 is a hydrophophic substituent.

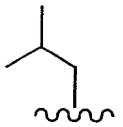
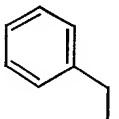
54. (New) The method of claim 53, wherein each of R, R^1, R^2 and R^3 is independently selected from the group consisting of

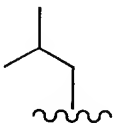
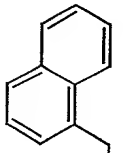


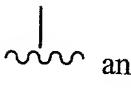
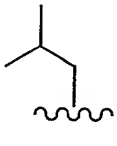
55. (New) The method of claim 53, wherein R^2 and R^3 are  and the compound is selected from the group consisting of

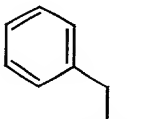
compound 1 (R^I=  and R= ),

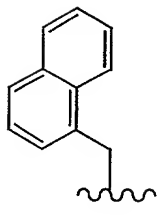
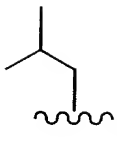
compound 2 (R^I=  and R= ),

compound 3 (R^I=  and R= ),

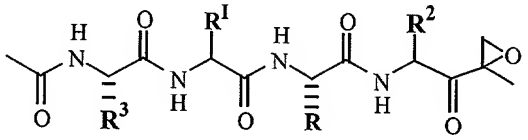
compound 4 (R^I=  and R= ),

compound 5 (R^I=  and R= ),

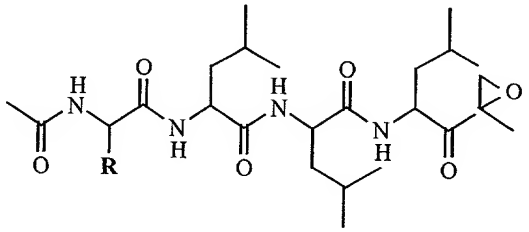
compound 6 (R^I=  and R= ) and

compound 7 (R^1=  and R= ).

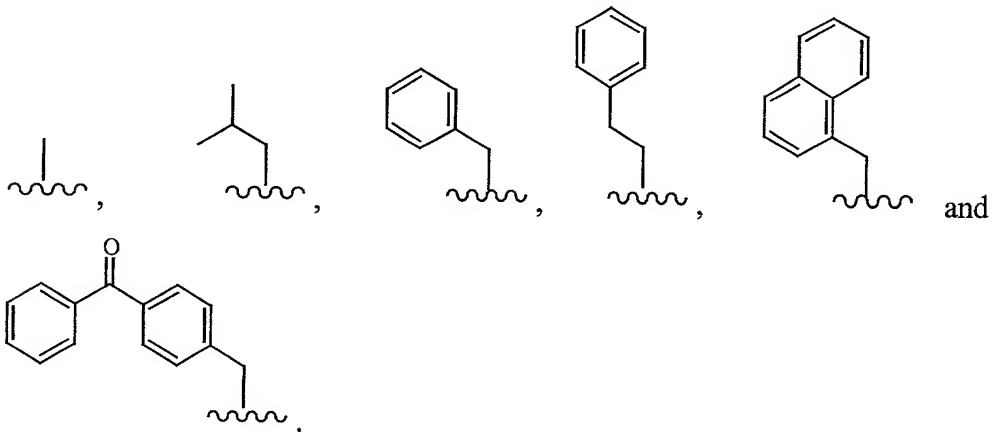
56. (New) The method of claim 53, wherein the peptide α', β'-epoxyketone has the following stereo-configuration:



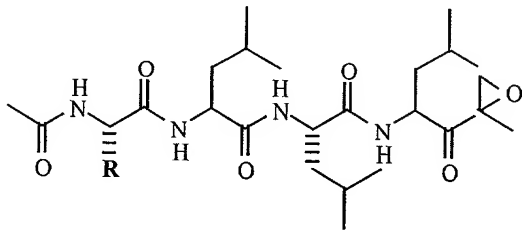
57. (New) The method of claim 49, wherein the peptide α', β'-epoxyketone has the following formula:



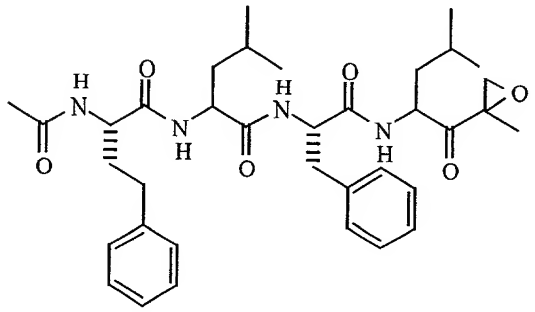
wherein R is selected from the group consisting of



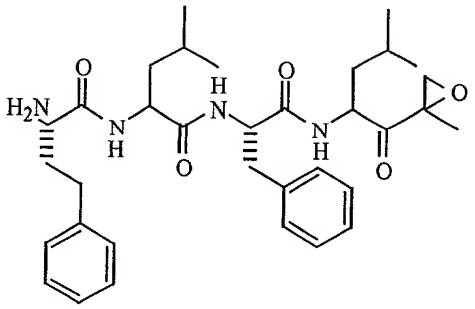
58. (New) The method of claim 57, wherein the peptide α', β'-epoxyketone has the following stereo-configuration:



59. (New) The method of claim 58, wherein the peptide α', β'-epoxyketone is

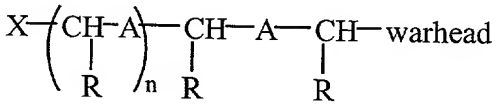


60. (New) The method of claim 45, wherein the compound is selected from the group consisting of



, PS-341, NLVS, PSI epoxide, lactacystin and PTX.

61. (New) The method of claim 45, wherein the compound has the following formula:



wherein the warhead reacts irreversibly with the catalytic chymotrypsin site of the proteasome;

A is independently CO-NH or isostereomer thereof;

R is independently a hydrocarbyl;

X is a polar group; and

n = 0-2.

62. (New) The method of claim 61, wherein R contains a substituted group selected from the group consisting of a halo group, -OR, -SR, $-NR_2$, =O, -COR, -OCOR, -NHCOR, $-NO_2$, -CN, and $-CF_3$.

63. (New) The method of claim 61, wherein X is protected.

64. (New) The method of claim 25, wherein said subject is a human.

65. (New) The method of claim 25, wherein said condition to be treated is selected from the group consisting of male pattern baldness, alopecia caused by chemotherapy, hair thinning due to aging, and genetic disorders.

66. (New) The method of claim 1, wherein said subject is a non-human mammal.

67. (New) The method of claim 66, wherein said hair growth provides additional protection from cold temperatures.

68. (New) The method of claim 25, wherein said hair growth is due to thickened hair sheath diameter, increased hair diameter, differentiation of quiescent hair follicles into more mature forms, increased rate of growth in hair length and/or thickness, or the appearance of proliferation of new hair follicles.

69. (New) The method of claim 25, wherein said compound is co-administered with an agent promoting skin tissue growth or infiltration.

70. (New) The method of claim 69, wherein said agent is selected from the group consisting of an epidermal growth factor, a fibroblast growth factor, a platelet-derived growth

factor, a transforming growth factor, a parathyroid hormone, a leukemia inhibitory factor, and an insulin-like growth factor.

REMARKS

Upon entry of the present Preliminary Amendment, claims 25, 27 and 45-70 will be pending. New claims 45-70 have been added. Support for the amended and new claims can be found throughout the application and *inter alia*, in original claims 3-21 and 44, and in the specification at page 8, lines 10-22, page 15, lines 25-29, page 24, lines 17-18, page 29, line 28 through page 33, line 15, page 9, lines 3-18, page 10, lines 19-22, page 11, line 30 through page 12, line 5, and in Examples 8-16. No new matter has been introduced by the present amendments.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing 432722002612. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 15, 2002

Respectfully submitted,

By: _____

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EXHIBIT A. VERSION WITH MARKINGS TO SHOW CHANGES MADE

25. (Amended) A method to treat a mammalian subject for a condition benefited by stimulating hair growth which method comprises administering to said mammalian subject in need of such treatment an effective amount of a compound [that inhibits the activity of NF-κB or] that inhibits proteasomal activity or that inhibits production of [these] proteasome proteins.